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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/578,438	03/21/2007	Ajay Verma	044508-5008-US	6971

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MORGAN LEWIS & BOCKIUS LLP
1111 PENNSYLVANIA AVENUE NW
WASHINGTON, DC 20004

EXAMINER	
LOVE, TREVOR M	
ART UNIT	PAPER NUMBER
1611	
MAIL DATE	DELIVERY MODE
09/09/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/578,438	VERMA ET AL.	
	Examiner	Art Unit	
	TREVOR M. LOVE	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 May 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,11,13-15 and 18-38* is/are pending in the application.

4a) Of the above claim(s) *1-5 and 18-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11, 13-15, 24-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgement is made to Applicant's response filed 05/04/2009.

Claims 1-5, 11, 13-15, and 18-38 are pending. Claims 1-5 and 18-23 are withdrawn. Claims 11, 13-15, and 24-38 are currently under consideration.

Applicant has overcome the rejection under 112, first paragraph, by incorporating the limitation of "human" into claim 11. Therefore, the rejection under 112, first paragraph, has been withdrawn.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 11, 13-15 and 24-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Teichberg (US PreGrant Publication 2006/0024284) as evidenced by Aminova et al (Pro-survival and pro-death effects of HIF-1α stabilization in a murine hippocampal cell line) and Lu et al (Hypoxia-inducible factor 1 Activation by Aerobic Glycolysis Implicates the Warburg Effect in Carcinogenesis).

Teichberg teaches a method of reducing extracellular brain glutamate levels by delivering a therapeutic amount of an active (see Abstract). Said composition comprises an active agent that is taught as being oxaloacetate diethylester (see [0025]). Alternate active agents are taught as being oxaloacetate, pyruvate, α-ketoisocaproate, α-ketoisovalerate, α-keto-β-methylvalerate (see [0025]), this reads on **instant claims 11**

and 34-38. Teichberg teaches that the preferred subjects of said method are canines, felines, ovines, porcines, equines, bovines, and humans (see [0102]), this reads on the limitation of "human subject" in **instant claim 11**. Said method is also taught as being useful for reducing brain glutamate levels in patients having coronary artery bypass surgery, which is a treatment for severe atherosclerosis. Furthermore, a patient having said surgery would necessarily be in need of wound healing (see claim 61), this reads on **instant claims 13-14**. Teichberg teaches that the composition can be applied topically (see [0126] and [0134]), this reads on **instant claim 15**. Teichberg also teaches that the composition can be administered rectally via enemas (see [0146]), by the nasal route via a spray (see [0142]), orally via a capsule (see [0140]), ocularly via intraocular injection, which would encompass solutions and suspensions (see [0133] and [0144]), and subcutaneously via an injection of a pharmaceutical composition which comprises a carrier (see [0133] and 0127]), these read on **instant claims 24-26, and 27, 28, 29, 30, and 31, respectively**. Teichberg identifies that the composition can comprise lipophilic solvents or vehicles such as fatty oils when the composition is being administered parenterally (see [0144]), the scope of parenterally includes transdermal, this reads on **instant claim 32**. Teichberg identifies that in certain scenarios, for instance, in brain surgery, the composition is sometimes preferably applied topically (see [0126]). Teichberg also discloses that the composition can be administered in a plurality of administrations over several days or weeks and that a skilled artisan would be able to vary the amount in order to meet the specific needs of the scenario (see [0152] and [0153]), this reads on **instant claim 33**.

Teichberg fails to directly disclose the relationship between the glutamate concentration and HIF-1 mediated gene expression.

Aminova teaches that HIF levels are higher at reduced glutamate levels (see Aminova, figure 5c). Lu teaches that pyruvate regulates hypoxia inducible gene expression independently of hypoxia by stimulating the accumulation of HIF-1α (see Lu, abstract).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize the composition of Teichberg in amounts significant enough to induce HIF-1 mediated gene expression since Teichberg teaches a composition for the reduction of glutamate, and Aminova teaches a relation between the concentrations of glutamate and HIF. There would be a reasonable expectation that Teichberg would use an effective amount of glutamate to induce HIF-1 mediated gene expression based on the evidence shown in figure 5c of Aminova wherein the relationship is identified.

With regard to the method of utilizing the composition being directed to promoting tissue neovascularization, it has been established that the composition is taught by Teichberg to be utilized on patient who are having coronary artery bypass surgery, which, like any major surgery, would require wound healing. Teichberg is teaching that the actives utilized in Teichberg reduce the amount of glutamate, which is useful for patients that are having surgery. Aminova provides evidence that as glutamate levels decrease, HIF increases. Therefore, the patient in Teichberg whose glutamate levels are decreased would necessarily show increased HIF-1 expression, particularly in view

of the evidence provided by Aminova that when glutamate levels are decreased, HIF increases. Furthermore, the instant claims recite neovascularization occurs when the claimed compounds are utilized in effective amounts to induce HIF-1 mediated gene expression. Hence, since the composition of Teichberg would induce HIF-1 mediated gene expression, there would also necessarily be neovascularization occurring in the patient with whom the composition of Teichberg is being administered. Furthermore, since a composition can not be separated from its properties, the composition as defined by the obvious combination set forth above would necessarily promote tissue neovascularization.

Response to Arguments

Applicant argues in the response filed 05/04/2009 that the Office fails to provide a reasonable basis for a link between HIF-1 mediated gene expression, administration of 2-oxoacids, and tissue neovascularization. Applicant argues that the two evidentiary references also fail to suggest a link between HIF-1 mediated gene expression and neovascularization. Applicant's argument is not found persuasive. The composition of Teichberg is similar, if not the same as the instant invention, further, the composition is taught as being delivered in similar, if not the same methods as the instant invention, and even further, the patient population is the same as the patient population of the instant invention. Therefore, the composition of Teichberg upon administration would necessarily induce HIF-1 mediated gene expression and neovascularization. Applicant further argues that "[t]he doctrine of inherency cannot be used to fill any gaping holes in the obviousness analysis". Applicant's argument is not found persuasive since the

composition, method of delivery, and patient populations are the same, the inherent properties of the composition are appropriately relied upon to provide evidence that the same effects (neovascularization) would necessarily occur. Applicant also argues that Teichberg teaches a laundry list of agents that are effective in reducing extracellular brain glutamate levels. Applicant's argument is not found persuasive since the list in paragraph [0025] of Teichberg includes only 22 specific compounds. It would be within the skill of one of ordinary skill in the art to test for optimum positive effects of delivery of each of said compounds. Applicant argues that pyruvate is taught as significantly increasing the plasma glutamate concentration, while oxaloacetate significantly reduces plasma glutamate, and Applicant argues that the Examiner has provided no reasonable expectation of success since pyruvate and oxaloacetate were observed to have opposite effects. Applicant's arguments are not found persuasive since Teichberg clearly teaches the use of both pyruvate and oxaloacetate in combination on multiple occasions (see Teichberg, [0017], [0022], [0025], etc). It is further noted that paragraph [0022] states that "the pharmaceutical composition comprising, as an active ingredient, pyruvate and oxaloacetate in a concentration suitable for reducing glutamate levels and a pharmaceutically acceptable carrier." Applicant further argues that just because a claimed species is encompassed by the prior art is in itself insufficient to establish *prima facie* obviousness. Applicant's argument is not found persuasive since, though Applicant is correct that a mere teaching of a component is insufficient to establish a *prima facie* case, Teichberg is being relied upon for more than a mere recitation of a component. Teichberg clearly teaches similar, if not the same components, the same

methods of delivery, and the same patient population, therefore, the reliance upon Teichberg is proper. Applicant further argues that "[i]n the absence of a disclosure in the prior art that suggests that the claimed method is obvious, the inherent properties of a composition cannot be relied upon for the invalidity of a method." Applicant's arguments are not found persuasive. The reliance upon the inherent properties of the composition are appropriate since the composition, methods of delivery, and patient population are similar, if not the same. Applicant further argues that the composition of Teichberg would not necessarily result in HIF-1 gene expression and accordingly would not necessarily result in tissue neovascularization. Applicant's argument is not found persuasive since the Examiner has set forth logic as to why the composition of Teichberg would result in HIF-1 gene expression, and therefore, neovascularization, and Applicant has merely alleged that the composition would not have the inherent feature. Therefore, Applicant's arguments are not found persuasive. It is noted that MPEP 2112 states: "Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977)." It is further noted that It is further noted that the art is not required to teach the same reasoning for adding components as Applicant, MPEP 2144 (IV) states "the reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by

Applicant. See, e.g., In re Kahn, 411 F.3d 977, 987, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006)."

Conclusion

No claims allowed. All claims rejected. No claims objected.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TREVOR M. LOVE whose telephone number is (571)270-5259. The examiner can normally be reached on Monday-Thursday 7:30-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila Landau can be reached on 571-272-0614. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

TL

/Gerald G Leffers Jr., PhD/
Primary Examiner